Scale-Up Considerations in the Fluid-Bed Process for Controlled-Release Products

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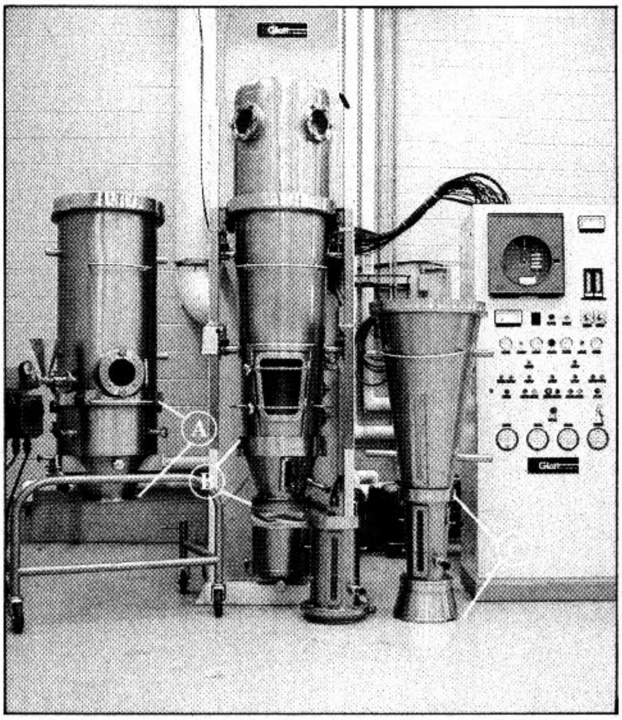
The three fluid-bed processes that can be used in manufacturing controlled-release products are reviewed in this article, and the process variables that should be optimized in the scale-up of fluid-bed processes are examined. Such variables include the spray rate, the pressure of the atomization air, the temperature of the inlet air, the volume of the fluidization air, the batch size, and the type of equipment that is used. Because such parameters can easily alter the end performance of the controlled-release product, they should be carefully investigated during the scale-up operation.



Courtesy of Glatt Air Techniques

Research-scale granulator–coater with three inserts and expansion chambers for tangential-spray coating (A), top-spray coating (B), and bottom-spray coating (C).

The coating of particulates such as powders, granules, pellets, and tablets to produce controlled-release dosage forms is becoming increasingly popular mainly as a result of recent advances in fluid-bed processors and in the development of both aqueous and organic solvent-based polymeric coating systems. This popularity, however, has also placed a greater emphasis on an effective scale-up program for such products because coating morphology and functionality can be easily affected by the variables of the fluid-bed process. For this reason, it is necessary to determine the effects of these process variables on the performance of the end product and to optimize the process and formulation variables.

Three fluid-bed processes can be used to apply polymeric films to produce controlled-release products. The first is a top-spray process used with a conventional granulator–coater, as shown in Figure 1. The second is a bottom-spray process used with a Wurster air-suspension column, as shown in Figure 2. The third process, shown in Figure 3, is a tangential-spray technique for use with a rotary fluid-bed granulator. The optimization of process variables, as well as the effects of the variables on the properties of the polymer film, depend to a large degree on the type of fluid-bed process that is used.[1-3] The three fluid-bed processes offer different advantages and disadvantages, as shown in Table I, and consequently the performance requirements of the finished product and suitable volumes of the product must be considered when selecting a coating process for a particular product.

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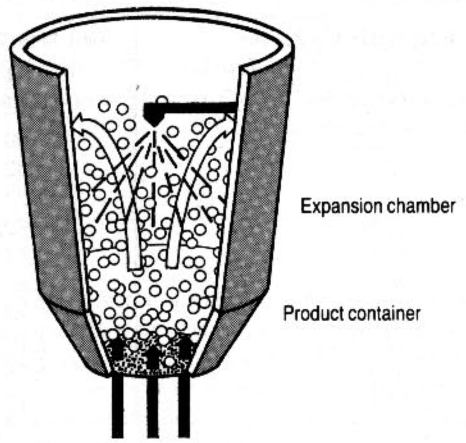

Figure 1: Top-spray method used in conventional granulation coaters.

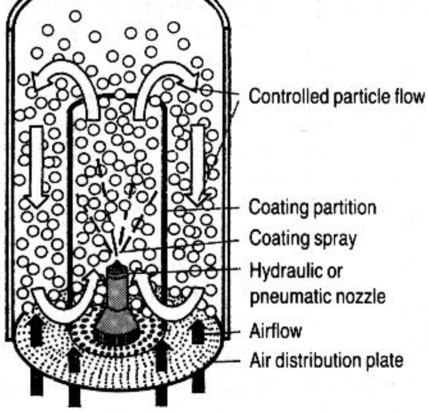

Figure 2: Bottom-spray method used in Wurster air-suspension columns.

The process parameters that are established for the scale-up program must be determined specifically for the particular spraying mode, size, and type of fluid-bed processing equipment that is selected. For instance, the spray rate that is established for the bottom-spray process might not be optimal for the top-spray or tangential-spray processes. This also might be true for other variables such as inlet-air temperature, fluidization air volume, and atomization air pressure. For this reason, the fluid-bed process should be selected during the product development phase rather than the scale-up phase, so that economic and regulatory concerns can be addressed adequately. However, in certain circumstances it might be economically advantageous to examine alternate spray modes during scale-up.

Process Variables

In addition to the method of spraying, almost 20 other variables are involved in the fluid-bed coating process for controlled-release products. To avoid expending excessive amounts of time during the scale-up phase, it might be necessary to prioritize these variables. Besides the mode of spraying, the most significant variables are the spray rate, the atomizing air

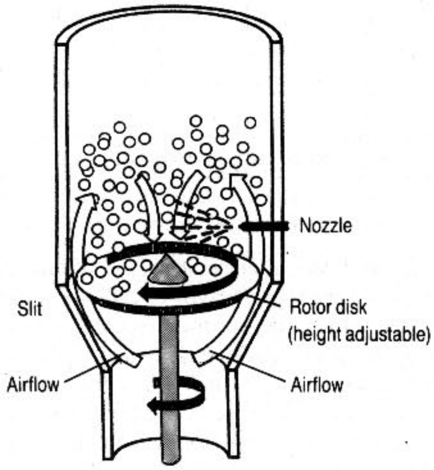

Figure 3: Tangential-spray method used in rotary fluid-bed coaters.

Table I: Characteristics of three fluid-bed coating processes.

Processing Method	Advantages	Disadvantages	Applications
Top-spray coating (conventional mode)	Accommodates large batch sizes, is simple to set up, and allows easy access to nozzle	Limited in its applications	Hotmelt coating and aqueous enteric coatings Not recommended for sustained-release products
Bottom-spray coating (Wurster)	Accommodates moderate batch sizes, produces uniform and reproducible film characteristics, and allows for widest application range	Tedious to set up, does not allow access to nozzles during processing, and is the tallest fluid-bed machine for coating fine particles	Sustained-release, enteric-release, and layering Poor for hotmelt coating
Tangential-spray coating (rotary mode)	Simple to set up, allows access to the nozzle during processing, permits higher spray rates, and is the shortest fluid-bed machine for coating fine particles	Puts mechanical stress on the product	Very good for layering, sustained-release, and enteric-coated products Hotmelt coating possible Not recommended for friable products

Table II: Approximate scale-up factors for granulators using top-spray coating.			
Unit Volume (L)	**Screen Diameter (mm)**	**Spray Rate Scale-Up Factor**	**Run Time Factor**
1.75	100	0.21	0.38
4.50	150	0.47	0.44
22	220	1.0	1.00
45	350	2.5	0.82
100	500	5.2	0.87
215	730	11.0	0.89
420	900	16.7	1.14
670	1000	20.7	1.47
1020	1150	27.3	1.70
1560	1250	32.3	2.20
2200	1750	63.3	1.58
3000	1740	62.6	2.18

Table III: Approximate scale-up factors for Wurster fluid-bed processors using bottom-spray coating.					
Wurster Column Size (in.)	**Partition Length (in.)**	**Batch Size (kg)***	**Volumetric Capacity (L)**	**Spray Rate Scale-Up Factor**	**Process Time (min)**
9	12	8	9.4	1.0	27
12	15	18	21	1.78	34
18	24	64	75	4.00	54
32	30	257	300	12.64	68
46	36	612	700	26.12	79

*Bulk density of the product is 0.85 g/cm^3

pressure, the inlet-air temperature, the volume of the fluidization air, the batch size, the type of equipment used, the nozzle height, the drying time, and the effect of moisture.

Spray rate. Scale-up of the spray rate is generally more critical in the coating process than it is in the granulation process. The primary objective of particle coating is to envelop each particle with sufficient coating material to achieve the desired function. To accomplish this, the size of the coating droplets must be kept small relative to the size of the particle that is to be coated. The liquid spray rate, at a given atomization air pressure and volume, affects the size of the droplets. Although increasing the liquid spray rate increases the droplet size, this also allows for a reduction in the processing time that is necessary.

In the coating process, the scale-up is not determined directly by the increase in batch size but generally is based on the increase in air volume, which can be determined in two ways. First, if both fluid-bed processors — the lab machine from which the process is being scaled and the pilot or production machine — have air-volume indicators, the spray rate multiplier can be determined as the ratio of the two air volumes that are required to give an adequate fluidization pattern in each machine. If the two machines do not have air-volume indicators, an approximation of the spray rate multiplier can be made using the ratio of the cross-sectional areas of the product bowl screens. This assumes, however, that achieving similar fluidization patterns in both pieces of equipment will require the same air velocity through the bowl screen.

Consider the following examples that illustrate the two alternatives available for determining the spray rate factor in scale-up procedures. In the first, a laboratory-scale fluid-bed processor has a batch size of 7.0 kg, a spray rate of 50 mL/min, and an air volume of 100 cfm. The scaled-up machine has a batch size of 350 kg and an air volume of 2700 cfm. The air volume for the batch size of 350 kg increases by 27 times, and the spray rate would be calculated as follows:

$$\frac{V_1}{V_2} \times S_2 = S_1 \tag{1}$$

where

V_1 = air volume in the scaled-up machine
V_2 = air volume in the laboratory-scale machine
S_1 = spray rate in the scaled-up machine
S_2 = spray rate in the laboratory-scale machine.

Using the values given above, the spray rate in the scaled-up machine would be 27 × 50 mL/min, or 1350 mL/min.

In the second example, the laboratory-scale fluid-bed processor has a batch size of 7.0 kg, a spray rate of 50 mL/min, and a product container with a cross-sectional area (πr^2) of 0.44 sq ft. The production-scale machine has a batch size of 350 kg and a product container with a cross-sectional area of 11.9 sq ft. The spray rate of the larger machine would be calculated as follows:

$$\frac{A_1}{A_2} \times S_2 = S_1 \tag{2}$$

where

A_1 = cross-sectional area of the scaled-up machine
A_2 = cross-sectional area of the laboratory-scale machine.

This equation assumes that the air velocity is roughly the same in

Table IV: Influence of ambient air conditions on drying capacity.

Inlet-Air Temperature (°C)	Ambient Air Dew Point (°C)	Total Heat (enthalpy) (kJ/kg of dry air)
25	1	38
25	12	51

each machine — that is, that their fluidization patterns are similar. Using the values given in the second example, the spray rate in the scaled-up machine is also found to be 1350 mL/min. The accuracy of these methods is dictated to a great extent by the tackiness that is inherent in the coating substance, which is often a limiting factor in coating small particles.

The spray rate factor also will be determined by the size of the particles of the substrate, the viscosity and nature of the liquid to be sprayed, and the temperature of the product. Although it is possible (and quite tempting) to reduce the processing time by increasing the spray rate to its maximum level — which does not cause agglomeration — it has been demonstrated in the literature that the dissolution rate of the drug can be affected by the spray rate.[4] In addition, the atomizing air pressure that is selected might determine the spray rate in terms of the size of the droplets. Table II lists approximate scale-up factors for spray rates in conventional granulators, which use the top-spray process, and Table III lists the scale-up factors for spray rates in the Wurster column, which uses the bottom-spray process.

Atomization air pressure. The majority of the nozzles that are used in fluid-bed processors are binary — that is, the liquid is supplied at a low pressure and is atomized into droplets by air. As mentioned previously, it is necessary to minimize agglomeration and to provide uniform film characteristics by keeping the size of the droplets small relative to the size of the particles to be coated. In general, the higher the atomization air pressure, the smaller the size of the droplets at any given spray rate. Typically, the volume of atomization air in a 5-kg batch can approach 40 cfm; in a 60-kg batch, the volume of atomization air can be as great as 100 cfm.

The size and design of the fluid-bed equipment must also be considered when establishing the parameter of atomization air pressure. For example, pressures that do not affect the fluidization pattern of a Wurster particle coater with a long expansion chamber can blind the exhaust filters of a Wurster column that has a short expansion chamber. Furthermore, when applying a hotmelt coating, it is necessary to heat the atomizing air to prevent the congealing of liquid in the nozzle; however, the safety of the operator is an obvious concern in this procedure.

Inlet-air temperature. The fluidization air temperature is a key variable in the coating process. It is not unusual to arrive at numerical values for this variable that are similar in larger scaled-up batches and in smaller batches if proper air volumes and similar dew-point conditions are used. A low fluidization air temperature, however, might lead to a problem commonly known as the *weather effect.*[5] In a coating process that uses one or more organic solvents to apply a film, a low fluidization air temperature is often used because of the low heat of vaporization of the solvent. A problem might arise when the dew point of the fluidization air is allowed to vary as changes in the seasons occur.

As shown in Table IV, the total heat — or enthalpy — varies as the dew point of the air varies at a constant dry-bulb air temperature. This variation in the amount of heat in the air may cause problems in the formation of the film because film formation relies to some extent on the evaporation rate of the solvent, which in turn depends primarily on heat. Furthermore, when the dew point is at 12 °C and the dry-bulb temperature is at 25 °C, as shown in Table IV, the evaporative cooling that is provided by the solvent can reduce the temperature of the air in the coating zone to less than 12 °C, resulting in condensation of water, possibly onto the surface of the product. If the film is incompatible with water, which is usually the reason why organic solvents are used to apply a film, the characteristics of the film might be seriously affected.

To avoid the weather effect it is necessary either to control the dew point of the air or to raise the temperature of the fluidization air. If the product is sensitive to heat, the ambient air can be preconditioned to control its dew point and, therefore, its impact on the drying rate. If possible, it is preferable to use a much higher fluidization air temperature because this tends to minimize the weather effect. However, a very high inlet-air temperature can cause spray drying of droplets. Also, if the product remains too dry and hence is subject to attrition, the product yield can decrease. With certain thermoplastic polymeric systems a very high inlet-air temperature can also cause agglomeration. The most desirable setting for the inlet-air temperature is one that allows for equilibrium between the application of the solvent as a liquid and its subsequent evaporation so that the film forms properly. For this reason, the heats of vaporization of any solvents that are present in the coating system must be taken into consideration when selecting the inlet-air temperature.

In many instances it might be necessary to optimize the temperature of the product based on the properties of the substrate and the coating. It is not unusual to find that the inlet-air temperature must be altered to arrive at similar product temperatures in different equipment. For this reason, monitoring the temperature of the product bed during scale-up might prove to be worthwhile.

Fluidization air volume. In fine-particle coating, an essential condition is a high particle velocity during spraying. In the top-spray and bottom-spray processes, the particles travel at a high speed past the nozzle and into an expansion area, where they dry. If the coated particles are forced to decelerate in a filter — which is the case in standard equipment — the coating can be damaged or transferred to the filter. If enough coating adheres to the filter, eventually the permeability of the filter will be reduced severely; the resulting reduced airflow and particle velocity will lead to agglomeration.

An air-volume indicator should be used to monitor airflow. Although an adjustable damper typically is used to control the fluidization air volume, occlusion of the outlet-air filter or of the product-bowl screen can cause resistance to airflow, and this might not be noticed unless the processor is equipped with an air-volume indicator. Because changes in air volume affect the fluidization pattern as well as heat exchange — that is, evaporation of the solvent and drying of the product — such changes might also affect the film formation process and consequently the performance of the finished product. Furthermore, an air-volume indicator aids in the determination of spray rate scale-up factors, as described earlier in this article.

Batch size. Batch size is a variable that infrequently requires attention or adjustment. To determine batch sizes for scale-up, the bulk density of the substrate is multiplied by the working volume of the processor, as shown in the following examples.

For top-spray coating in conventional granulators, maximum and minimum batch sizes are determined using the following equations:

$$S_{max} = V \times 0.8 \times BD \qquad (3)$$

$$S_{min} = V \times 0.5 \times BD \qquad (4)$$

where

S = batch size

V = volume of the container

BD = bulk density of the substrate.

For bottom-spray coating in Wurster columns, the batch size for coating particles is calculated as follows:

$$S_{max} = (\pi R_1^2 H - N\pi R_2^2 H) \times BD \qquad (5)$$

$$S_{min} = {}^1/_2(\pi R_1^2 H - N\pi R_2^2 H) \times BD \qquad (6)$$

where

R_1 = radius of the chamber

R_2 = radius of the partition

N = number of partitions

H = length of the partition.

The batch size for coating tablets when using the bottom-spray coating process is calculated using the following formula:

$$S = (\pi R_1^2 H - {}^1/_2 N\pi R_2^2 H) \times BD. \qquad (7)$$

For tangential-spray coating in rotary fluid-bed granulators, maximum and minimum batch sizes are determined as follows:

$$S_{max} = V \times 0.8 \times BD \qquad (8)$$

$$S_{min} = V \times 0.2 \times BD. \qquad (9)$$

Type of equipment. Ideally, the type of fluid-bed equipment to be used should be selected during the product development phase. However, if circumstances do not permit this and equipment must be selected during the scale-up phase, several factors must be considered. For example, the length of the expansion chamber is related to the type of product to be coated — whether powders, granules, pellets, or tablets. Because the position of the outlet temperature probe varies in different types and sizes of equipment, it is strongly recommended that the process be monitored with a product temperature probe. Because the process is isothermal, the position of the product probe generally is not critical. In addition, a product temperature probe is much more responsive because it measures only the temperature of the product and is not affected by the temperature of its surroundings, as is the outlet temperature probe.

Mode of spraying. The importance of selecting the mode of spraying and its effect on the performance of the product has been discussed earlier in this article and in the literature.[1,2] The need for caution in selecting a mode of spraying cannot be overemphasized for products that are coated for controlled release using the fluid-bed process.

Nozzle height. Although many products are coated using the top-spray method, the bottom-spray and tangential-spray methods might be more logical approaches for coating fine particles. In a conventional top-spray fluid-bed coater, it is possible to minimize the size of the coating zone — the region through which droplets must travel — by positioning the nozzle at the shortest possible distance from the static bed. This maximizes the concentration of particles in the coating zone. To increase the rate of application in larger batch sizes, it might be necessary to increase the number of coating zones in pilot- or production-scale coaters. This is usually accomplished by using a multi-headed nozzle in top-spray equipment, multiple partitions and nozzles in bottom-spray equipment, or multiple nozzles in tangential-spray equipment.

Drying time. The effect of drying time on the performance of the end product is more critical when latex or pseudolatex films are applied for controlled release. This is because the rate and degree of coalescence depend not only on the temperature of the drying air but also on the length of the drying phase. In addition, the amount of solvent residue — aqueous or organic — also depends on the amount of drying time.

Effect of moisture. The heat content of moist air is greater than that of dry air, and variation in heat content can result in different release profiles, depending on the types of solvents and polymeric systems that are used in the coating process. Residual water in the coating layers of particles or tablets might affect the film forming process. For this reason, the effect of ambient air dew points should be examined as a part of the scale-up program in organic solvent processes as well as in aqueous coating operations.

Other scale-up considerations in the production of controlled-release dosage forms — such as formulation variables and physicochemical properties of the substrate — are beyond the scope of this article. Nevertheless, the impact of these considerations on the overall success of the scale-up program should not be underestimated. These factors have been discussed briefly in the literature.[6]

Conclusion

Fluid-bed processors that have been developed recently offer a unique opportunity to develop and produce coated controlled-release products. However, various process parameters, such as those discussed in this article, easily can alter performance of the product and hence should be examined thoroughly during the scale-up phase. Unfortunately, researchers have not yet gathered enough experience in this area, and continued investigation is needed. The interplay of various processing parameters presents a great challenge in optimizing the coating process, and continuing efforts to investigate and understand this interplay are extremely necessary in order to ensure the reproducible performance of controlled-release products.

Acknowledgment

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